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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
SCHNIZER,H	
ART UNIT	**PAPER NUMBER**
1653	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary	Application No. 09/819,260	Applicant(s) LIPOVSEK ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-67* is/are pending in the application.

4a) Of the above claim(s) *1-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3&5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group III, Claims 40-67 in the Response to the Restriction Requirement filed June 25, 2001 (Paper No. 7) is acknowledged.

Status of the Claims

2. Claims 1-67 are pending. Claims 1-39 are withdrawn from further consideration as being drawn to a non-elected invention. Claims 40-67 have been considered on the merits in this Office Action.

Drawings

3. The drawings filed February 29, 2000 are objected to for reasons cited on the Form PTO 948.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 40-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claims 40-67 are unclear as to what sequences are considered randomized since the claims do not contain a template sequence with which to compare. The

specification defines randomized as "including one or more amino acid alterations relative to a template sequence (see p. 9, lines 1-2). Many proteins contain fibronectin type III domains and the amino acid sequences of these domains vary even within one species. Thus, for example, one might view tenascin (comprising a type III domain) as a protein within the metes and bounds of the claims because it contains loops having amino acid alterations (randomized) as compared to a particular fibronectin sequence. On the other hand, another might view tenascin outside the metes and bounds of the claims because as compared to its own fibronectin type III domain, there are no amino acid alterations (no randomized loop). Addition of a template sequence with which to determine if a loop was randomized would clarify this matter.

4. The term "randomized" in Claims 40-42 and 59 is also unclear because the term generally refers to libraries of proteins. For example, Koide et al. (J. Mol. Biol. (1998) 284: 1141-1151; referenced in IDS of Paper No. 5) states that they prepared a library of FN3 in which residues in two loops were randomized (see abstract). One of skill in the art would understand this statement to mean that individual proteins in the library contained unique sequences relative to the other proteins of the library. Thus, the loop contains random sequences across the library. The confusion caused by this inconsistency is further illustrated in the enablement rejection below. It appears that applicant may have intended to claim a method of screening a library of proteins.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 40-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

7. Applicant is referred to the interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 4, pp. 1099-1111 (available at www.uspto.gov) and the Examiner training Materials on Written Description also available at www.uspto.gov.

8. The claimed genus includes a method of obtaining any compound or protein, wherein the protein comprises a fibronectin type III domain having at least one randomized loop, by contacting the compound and protein under conditions that allow complex formation, and obtaining from the complex, the compound or protein. The specification defines "randomized" as including one or more amino acid alterations relative to a template sequence (see p. 9). Therefore, there are no limitations on how many amino acid residues can be substituted, inserted, or deleted and there are no limitations on what amino acid positions can be modified. Thus, the claimed genus includes a method of obtaining any compound or protein by any binding assay.

9. When there is substantial variation within the genus (as in the present case), one must describe a sufficient variety of species to reflect that variation. In the present case, the claims are broadly drawn so that they encompass any protein binding method wherein the protein used in the method contains at least one loop. The claims

encompass methods using proteins having any binding activity or enzymatic activity and almost any structure (in addition to the "at least one randomized loop"). Thus, there is infinite variation in the claimed genus. The specification does not contain any actual reduction to practice of a method of obtaining an individual protein or compound by contacting a single protein and compound under conditions to allow complex formation and then obtaining either the individual compound or protein. The specification vaguely describes screening a library of proteins containing three randomized loops of the 10th module of a type III fibronectin domain for TNF-α binding activity. The specification indicates that a percentage of the proteins of the library bound TNF-α (see Figure 10) but does not describe any individual protein that binds TNF-α by any identifying characteristics and does not even describe obtaining any particular protein from the protein-TNF-α complex. The specification does not provide any guidance as to the structure (amino acid sequence) of a TNF-α binding protein because the specification does not provide its amino acid sequence or even what amino acid positions of the fibronectin type III domain were randomized in the protein library used to isolate the TNF-α binding protein. The specification does not provide any reduction to drawings of any proteins that would be encompassed by the claimed genus or any relevant, identifying characteristics. In fact, the proteins used in the method of the claimed genus include any structure or function of interest.

10. Structural features that could distinguish the proteins used in the claimed method from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the claimed genus. The general knowledge and level

of skill in the art do not supplement the omitted description because specific guidance (such as which amino acid positions are randomized and which are not, and what compound the protein binds) not general guidance is what is needed. One of skill in the art would conclude that applicant was not in possession of the claimed genus because the specification fails to disclose any common attributes or characteristics that identify members of the genus, the genus is highly variant, and the specification provides only a single disclosed species and this species itself is not specifically described. Therefore, written description requirement for a claimed genus is not satisfied in the present case because the specification does not provide a sufficient description of a representative number of species.

11. Claims 48-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining a protein or compound which binds a protein or compound comprising contacting a protein comprising a fibronectin type III domain having at least one randomized loop under conditions that allow complex formation and obtaining the protein or compound from the complex, does not reasonably provide enablement for such a method wherein the compound binding is mediated by one, two, or three loops of the tenth module of the fibronectin type III domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

12. The specification has not taught how to practice the claimed method wherein the number of loops that are involved in binding can be predicted or controlled. Protein binding is dependent on structure. And, the state of the art is such that it is acknowledged that one cannot merely predict protein function (such as binding function) from amino acid sequence information. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation that they will provide a particular binding function is unpredictable. (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 14-16). Thus, even using library screening techniques, one of skill in the art would not know which loops and which amino acid positions within those loops should be randomized to achieve binding through a specific number of loops.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. Claims 40-47, 49, 52, 59, and 66 are rejected under 35 U.S.C. 102(a) as being anticipated by Koide et al. (J. Mol. Biol. (1998) 284: 1141-1151; referenced in IDS of Paper No. 5).

15. Koide et al. teach a method of obtaining ubiquitin (a protein and compound) which binds a protein comprising a fibronectin type III domain having at least one randomized loop (Ubi4). The method comprises contacting the ubiquitin with the protein under conditions that allow compound (or protein)-protein complex formation; and obtaining from the complex the protein or compound (ubiquitin) (see p. 1144-1145). The tenth module of the human FN3 domain is used in the disclosed method (p. 1142, Col. 1, beginning at line 9 from bottom). It appears that the ubiquitin binding is mediated by two FN3 loops (p. 1144, Table 1, and p. 1146, Col. 2). Koide et al. meet the limitations of Claims 42 and 43 since the reference teaches that the FN3 protein that bound ubiquitin was isolated and contributions of individual residues was tested by further randomization followed by repeating the steps of the binding assay (p. 1145, Col. 1, bottom paragraph). The FN3 mutant used in and isolated by the Koide et al. method lacks an integrin-binding motif (RGD)(p. 1144, Table 1). Thus, Koide et al. meets the limitations of the claims.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 40-41, 44-46, 56-57, and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Main et al. (Cell (1992) 71: 671-678; referenced in IDS of Paper No. 3) in view of Lee et al. (Protein Engineering (1993) 6: 745-754) and Nygren et al. (Curr. Opin. Struct. Biol. (1997) 7: 463-469; referenced in IDS of Paper No. 3).

18. Main et al. teach the structure of the tenth fibronectin type III domain which contains the FG loop that is solvent exposed and highly mobile (see abstract). Main et al. teaches that the FG loops have similar topology to the immunoglobulin C domains (see Figure 5 and p. 675). Main et al. state "[t]he structure presented in this paper gives insight into the way a functional loop can be built onto a structural framework and, by virtue of its flexibility, be able to perform a wide range of functions." (p. 676, Col. 2, lines 19-23).

19. While Main et al. suggest that a protein comprising a fibronectin type III domain having at least one randomized loop could be used in a method of obtaining a protein or compound, Main et al. does not specifically teach such a method.

20. Lee et al. teaches a design, construction, and binding analysis (method of obtaining a protein) of a series of mutants (randomization) in which amino acid sequences are inserted into the CDR loops in the immunoglobulin VL domain. Figure 7 of Lee et al., shows data from an ELISA assay for binding of biotinylated fibrinogen to the immunoglobulin protein. Lee et al. also state "[s]caffolds capable of displaying more than one sequence might be used to construct multifunctional molecules as well as reconstruct discontinuous binding surfaces such as those found in hormone receptor binding sites" (p. 753, Col. 1, last paragraph of "Discussion").

21. Nygren et al. review combinatorial approaches to obtain proteins using suitable starting proteins as scaffolds (including the use of immunoglobulins as scaffolds).

22. It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have practiced a method of obtaining a protein (a compound) using the fibronectin type III domain as taught by Main et al. as a scaffold for replacement of amino acid residues as taught by Lee et al.

23. One of ordinary skill in the art at the time of the invention would have been motivated and would have had a reasonable expectation of success to have used the fibronectin type III domain as taught by Main et al. as a scaffold for replacement of amino acid residues as taught by Lee et al. because Main et al. teach that the fibronectin type III topology is similar to that of the immunoglobulins and functional loops can be built onto a structural framework to be able to perform a wide range of functions. In addition, one of ordinary skill in the art at the time of the invention would have been motivated and would have had a reasonable expectation of success to have used the fibronectin type III domain as taught by Main et al. as a scaffold for replacement of amino acid residues as taught by Lee et al. because Lee et al. teach replacement of surface loops with amino acid sequences that bind to a receptor in an immunoglobulin domain with affinity in the nanomolar range. Moreover, one of ordinary skill in the art at the time of the invention would have known that the FG loop of FN3 has similar topology as CDR3 in an immunoglobulin (see figure 5 of Main et al.) and would have known that both of these loops are surface exposed. The skilled artisan would have had an expectation of success in replacing residues in the FG loop in FN3 because Lee et al.

had replaced residues in the CDR3 of REI, which is also a surface exposed loop. Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the FN3 domain of Main et al., which has a fold similar to the immunoglobulin of Lee et al., and replace residues in the surface exposed loops with residues that would bind to a binding partner as taught by Lee et al.

24. One of ordinary skill in the art at the time of the invention would have been motivated to use the FN3 domain, with at least one randomized loop, (as taught in Main et al. and Lee et al.) specifically in a method of obtaining a protein which binds the compound or protein because as was well known in the art (as evidenced in Nygren et al.) "the use of combinatorial approaches coupled with a powerful selection or screening strategy can be used to obtain novel proteins capable of binding a desired target molecule" (see Nygren et al., p. 467, Col. 2, first paragraph of "Conclusions").

25. Therefore, it appears that the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

26. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone

numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
September 1, 2001

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER